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MEDICAL HISTORY

Self-Experimenting Physicians
Mavericks or martyrs?

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الأطباء الذين يجرون التجارب على أنفسهم
المتفردون أم شهداء العلم؟

ريتو لكتاكيا و إكرام بيرني

Hope lies in dream, in imagination and in the courage of those who dare to make dreams into reality. Jonas Salk.[1]

What motivates a physician to inflict disease on his own person—the tenacity to establish the truth, a passion for research whatever the cost, frustration with unbelieving peers or sheer bravado in one's own invincibility? The history of medical discoveries is replete with tales of individuals whose pursuit of knowledge and self-belief prompted them to become human guinea pigs. The outcome of their self-experimentation ranged anywhere from mortality to a cure. Accolades, including the Nobel Prize, were the reward for a few. One thing is certain: their feats have become the lore of medical literature that generations of physicians will remember with astonishment and admiration. This article focuses on a recent notable example of the discovery of the bacterial origin of gastritis followed by a brief mention of other heroic exploits. Many of these are an inspiration to physicians when research efforts go unrequited and disappointments take their toll.

Dogma and Disbelief Demolished

In 2005, the Karolinska Institute in Stockholm, Sweden, awarded the Nobel Prize in Medicine or Physiology to J. Robin Warren and Barry J. Marshall for their discovery of a bacterial cause of gastritis and peptic ulcer disease.[2] The pathologist-physician duo were paid homage for the struggle they encountered in establishing a revolutionary concept—a bacterial aetiology in the pathophysiology of gastric disease. This recognition was almost an oddity in a century when awards were usually given for research on genes and subcellular biochemical processes.[3]

In his lecture during the Nobel Prize ceremony in December 2005, Warren eloquently quoted the fictional detective Sherlock Holmes: "There is nothing more deceptive than an obvious fact".[4] He was referring to the reaction of the medical fraternity when he initially proposed that a spiral-shaped bacteria could be found in the stomach. It defied the wisdom of the centuries which stated that the acid environment of the stomach could not possibly permit bacterial growth. H2-receptor antagonists, the commercial jackpot of the 20th century pharmaceutical industry, have acid-lowering capacities, but treat rather than cure ulcers.[5] Warren had first observed these bacteria in a gastric biopsy on 11 June 1979 (his 42nd birthday).[6] Bacteria had been seen by others in the gastric mucosa but they were largely considered to be contaminants. The implication that an infection caused stomach inflammation or ulcers contradicted the firm belief that lifestyle and stomach acidity were the culprits.[6] Warren's training as a pathologist, his passion for staining techniques (especially silver stains) and his persistence stood him in good stead when he doggedly pursued his discovery with other tools of the trade: electron microscopy and, later, bacterial cultures.

Warren's lonely two-year quest received a boost when, in 1981, a gastroenterology registrar, Marshall, became his clinical collaborator. The physician-pathologist partners took their research a step further with a systematic collection of gastric antral biopsies which allowed them to observe microscopic changes in symptomatic patients without the confounding histological changes that biopsies from ulcer edges produced. Their attempts to characterise the bacteria, referred to as *Campylobacter*-like organisms, were met with disappointment until a fortuitous failure

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to discard cultures over the Easter holiday in April 1982 resulted in colonies appearing on the culture plate.[7] This was the *Eureka* moment following many disappointing months of collecting and delivering specimens to the microbiology laboratory with a negative outcome. Routinely, culture plates had been discarded after 48 hours; however, the new bacterium needed five days to grow. The organism was later classified as *Helicobacter pylori*.[4]

In 1983 and 1984, Warren and Marshall published their findings in a prestigious medical journal, *The Lancet*, after stiff resistance from reviewers.[8,9] Initial reactions to these pioneering publications stood in sharp contrast to the laudatory interviews and expert editorials in leading scientific journals which followed when the duo's work was recognised by the Nobel Committee just over two decades later.[7,10,11] After the initial publications, worldwide interest grew rapidly; however, Marshall still had to convince disbelievers that *H. pylori* was the cause of gastritis and peptic ulcers, since no effective animal model had yet proven its pathogenicity.[5] In late 20th century medical practice, where ethical clearance for a human experiment was very difficult to come by, he decided to establish the disease in his own body. Marshall managed to obtain a pre-experiment endoscopic biopsy to establish baseline observations. To aid the bacteria in establishing themselves in his stomach mucosa, he reduced his stomach acid by consuming cimetidine, drank the bacterial culture and fasted for the rest of the day.[12] He developed bloating, nausea and vomiting with night sweats and halitosis after three days. The subsequent biopsy irrefutably established the bacterial presence on stains and cul-tures.[12] After 14 days, the symptoms and the bacteria vanished from the mucosal biopsies, apparently due to his own immune response. However, Marshall had fulfilled Robert Koch's postulates for identifying the causative agent of a disease and proven that the bacterium was a cause of gastric inflammation.[12]

Personal anecdotes marked this journey of discovery. Warren credits the support of his wife for helping him remain on course despite the deterrence meted by his peers.[10] Marshall's wife Adrienne had also noted his "putrid breath" in the wake of his drinking the *H. pylori* cocktail without her knowledge.[5] The bold experiment may have earned him marital disfavour, but was instrumental in generating an era of antibiotic treatment for gastritis disorders. *H. pylori* became the first bacteria to be linked to carcinogenesis (gastric adenocarcinomas and lymphomas) in the research that followed.[13]

The Heart of the Matter

Cardiac catheterisation appears today as a straight-forward, even routine procedure for a practicing cardiologist. But when the idea first gained momentum in the mind of a young German doctor, Werner Forssmann, in 1929, it was nothing short of revolutionary. Deriving inspiration from having witnessed the drawings of French physiologists who were able to access the heart chambers through the jugular vein in animals, he was convinced it was a workable idea.[14] He tested his theory by introducing a ureteric catheter through his brachial vein and into his heart. The unconventional step needed not only personal grit but also involved considerable artifice in convincing both the head nurse to part with sterilised instruments and the radiographer to record the historical moment.[14]

Not Always for the Right Reasons

Another bacterial experiment in the 19th century did not achieve the same success that Warren did with *H. pylori*. Max von Pettenkofer was Koch's antagonist and argued vociferously against contagion (infection) being the cause of disease.[15] As such, he opposed the public health water hygiene measures designed to prevent water-borne infections like cholera. In a desperate attempt to prove his point, he swallowed the cholera *bacillus*; since he fortunately failed to develop the disease, he felt vindicated in standing his ground despite his incorrect aetiological hypothesis.[15]

Team Spirit in Medical Experiments

From the fold of military medicine came the triumphant discovery that a mosquito, later identified as *Aedes aegypti*, was the vector of yellow fever. In 1900, Major Walter Reed, a surgeon in the USA Army, led the U.S. Army Yellow Fever Board to Cuba. Although he was one of the members, Reed himself did not submit to being bitten by infected mosquitoes and it was his compatriot, Jesse W. Lazear, who succumbed to infection in the search for truth.[16] Reed was hailed as a hero for saving countless lives in Havana, Cuba. However, the fact that many of his so-called volunteers were members of his team of health professionals casts a long shadow on the dynamic team leader who extracted a human cost from his intrepid followers. Another member of this loyal band was Clara Maass,

a 25-year old American nurse-volunteer, who also succumbed to the disease in 1901.[17]

Zealous researchers were sometimes not beyond including their family members in their crusades. Jonas Salk and his wife and children received the attenuated polio vaccine early in its trials, before millions of children known as 'Polio Pioneers' were officially tested in 1954 to determine the efficacy of the drug.[1]

Inspiration and Aftermath

Curiosity, convenience or self-conviction? Perhaps they all played complementary roles in driving these explorers to what may seem to be illogical risk-taking behaviours. Notably, 12 individuals who performed self-experiments—including Ramsay who exposed himself to anaesthetic gases, Lawrence who drank radioactive sodium, Metchnikoff who self-injected relapsing fever spirochaetes and Forssmann who performed self-cardiac catheterisation—were awarded Nobel Prizes, although not necessarily for these specific experiments. In an interesting review of auto-experimenters dating from 1800, 465 episodes came to light.[18] Tragically, at least eight self-experimenters died as a result of their research adventures in the field of infectious disease. Geographically, the self-experimenters were mostly from the USA (33%) followed by Germany (15%); in terms of gender, there were 12 women, the majority of whom were Russian.[18]

Conclusions drawn from such misadventures were sometimes misdirected. The famous Scottish surgeon, John Hunter, set out to straighten the record on gonorrhoea and syphilis. These were thought to be the same disease: the first visible by its urethral discharge, the second developing more systemic manifestations.[19] Reports that he self-infected himself with pus derived from the genital sore of a prostitute in 1767, succeeding in contracting both gonorrhoea and syphilis simultaneously, have been controversial. Nevertheless, these resulted in his putting forward a misleading conviction that these two sexually transmitted diseases were caused by a common pathogen which was later proven wrong.[19]

Self-Experimentation: *The 21st century avatar*

These instances detailed above beg the question—is self-experimentation relevant in the 21st century? In a recent exposition on the subject, Dresser argues for its revival in a modified form.[20] She supports the practice for the accuracy of self-observation, the lack of complete replication of the human situation in animal models and the clear academic and moral arguments for doing unto oneself before inflicting others. She even emphasises a leadership element, whereby medical professionals can lead by example before seeking informed consent from patients or healthy volunteers.[20] Additionally, Dresser points out hitherto undisclosed aspects of research she learnt as a volunteer, such as delays in treatment or the possibility of trials being prematurely stopped or remaining unfinished. In her own words, "Personal exposure led me to understand the heavy burdens such a duty would impose on seriously ill patients".[20] The institutional review boards and ethics committees of today do not always include this aspect of trials in their remits and may therefore need to expand their ambit.

What then is the way forward? It is our conviction that we have not seen the last of this breed of researchers who would risk all to pursue a strongly held hypothesis. It is equally certain that formal approval through ethical committees will be hard to obtain given the legal implications, with some experiments potentially being equated with suicide. Yet, if the experimenters survive to tell their tale, the scientific community invariably embraces the new fact. There is another alternative—leaders of research teams may do well to pay heed to out-of-the-box ideas from their mentees and allow them the latitude to confirm or dismiss them through experimentation, rather than self-experimentation. Lone rangers, however, may still make the critical decision to experiment on themselves, sometimes only to prevent an original idea from being plagiarised. Therein lie the dangers of the human frailties of possession and secrecy.

Lessons from the History of Self-Experimentation

Altruistic, audacious or simply foolhardy, these mavericks of medicine have earned veneration from the world in general and young physicians in particular. Medical pioneers and researchers who travelled this path through self-example and self-sacrifice have demonstrated the boldness and recklessness that creates legends. Adversity kept them undaunted in their mission; derision and mockery by their peers pushed them to bravado. Whether it earned them fame, notoriety or an untimely death, in many cases both clinical research and humankind have benefited from self-experimentation.

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